REMARKS

Claim Status

Claims 1-16, 18, and 20-34 were pending in the subject application. By this Amendment, applicants have amended claims 1-4, 6-11, 22, 24, 26, and 28-30, and cancelled claims 14, 21, 23, and 25 without prejudice or disclaimer. Accordingly, upon entry of this Amendment, claims 1-13, 15, 16, 18, 20, 22, 24, and 26-34 will be pending and under examination.

Support for amended Claim 1 may be found inter alia in the specification, as originally-filed, on page 5, line 6 through page 6, line 6; and page 3, lines 13-30.
Support for amended Claim 2 may be found inter alia in the specification, as originally-filed, on page 7, lines 3-4; and page 3, lines 13-30.
Support for amended Claim 3 may be found inter alia in the specification, as originally-filed, on page 7; lines 16-23; and page 3, lines 13-30.
Support for amended Claim 4 may be found inter alia in the specification, as originally-filed, on page 7, lines 25-32; and page 3, lines 13-30.
Support for amended Claim 6 may be found inter alia in the specification, as originally-filed, on page 8, lines 5-12; and page 3, lines 13-30.
Support for amended Claim 7 may be found inter alia in the specification, as originally-filed, on page 8, line14 through page 9, line 22; and page 3, lines 13-30.
Support for amended Claim 8 may be found inter alia in the specification, as originally-filed, on page 9, line 24 to 28; and page 3, lines 13-30.
Support for amended Claim 9 may be found inter alia in the specification, as originally-filed, on page 9, line 30 through page 10, line 2; and page 3, lines 13-30.
Support for amended Claim 10 may be found inter alia in the specification, as originally-filed, on page 10, line 30 through page 11, line 9; and page 3, lines 13-30.
Support for amended Claim 11 may be found inter alia in the specification, as originally-filed, on page 11, lines 11-14; and page 3, lines 13-30.

Claim 22 was amended to correct the dependency of claim 22 in light of the cancellation of claim 21.

Claim 24 was amended to correct the dependency of claim 22 in light of the cancellation of claim 23.

Claim 26 was amended to correct the dependency of claim 22 in light of the cancellation of claim 25.

Support for amended Claim 28 may be found inter alia in the specification, as originally-filed, on page 9, lines 26-28.

Support for amended Claim 29 may be found inter alia in the specification, as originally-filed, on page 9, lines 31-32.

Support for amended Claim 30 may be found inter alia in the specification, as originally-filed, on page 11, lines 6-9.

As the amendments to claims 1-4, 6-11, 22, 24, 26, and 28-30 raise no issue of new matter; applicants respectfully request that the amendment be entered.

Objection to the Specification

On page 2 of the March 5, 2007 Office Action, the Examiner objected the disclosure because of informalities. The Examiner indicates that applicants refer to "acidic acid" in the experimental procedures, and the Examiner has assumed that applicants have meant "acetic acid". The Examiner indicates that correction is required.

In response, and in an attempt to advance the prosecution of the instant application, applicants have amended the misspelled words "trifluoroacetic" and "acetic" in the experimental section of the present application.

Support for the amendments to the specification may be found inter alia in the specification, as originally-filed, on page 14, lines 11-20.

Accordingly, applicants respectfully request reconsideration and withdrawal of this objection.

Non-Statutory Obviousness-Type Double Patenting

On pages 3 of the March 5, 2007 Office Action, the Examiner rejected claims 1-14, 16, 18, and 20-34 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-4 and 6-11 of U.S. Patent No. 7,144,884 B2.

Applicants respectfully traverse the rejection, as it is well settled that the specification of US Patent No. 7,144,884 B2 ('884), does not qualify as prior art. 3 Donald S. Chisum, supra, § 9.03[3]; *In re Longi*, 759 F.2d at 892 n.4, 225 U.S.P.Q. at 648 n.4 (citing *In re Braithwaite*, 379 F.2d 594, 600, n.4, 54 C.C.P.A. 1589, 1597, n.4, 154 U.S.P.Q. 29, 34 (1967) and *In re De Blauwe*, 736 F.2d 699, 222 U.S.P.Q. 191 (Fed. Cir. 1984)).

Applicants note that '884 claims do not define Y=CH. Further, applicants note that all the examples in claims 5 and 12 of '884 have Y=N and X=S. In the rejection, however, the Examiner improperly refers to the specification of the '884 patent to support the case of obviousness-type double patenting. Because this reliance on the specification is not permitted under the doctrine (see above cites), this rejection should be withdrawn.

A determination of obviousness-type double patenting is close to a determination of obviousness under 35 U.S.C. § 103. *In Geneva Pharmaceuticals, Inc. v. Glaxosmithkline plc, Smithkline Beecham Corporation*, 349 F.3d 1373 (Fed. Cir. 2003). The Federal Circuit expressly rejected any generalized rule relating to *prima facie* obviousness in a case involving substitution of an oxygen linkage for a sulfur linkage. *In re Grabiak*, 769 F.2d at 732, 226 U.S.P.Q. at 872.

Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

On page 5 of the March 5, 2007 Office Action, the Examiner rejected claims 1-12, 14, 16, 18, and 20-34 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-6 and 8-17 of U.S. Patent No. 7,138,407 B2.

In response, without conceding the correctness of the Examiner's position and upon the indication of allowable subject matter in connection with the present application, applicants will consider filing a terminal disclaimer to overcome the obviousness-type double patenting rejection.

Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection Under 35 U.S.C. § 101

On pages 6 of the March 5, 2007 Office Action, the Examiner provisionally rejected claims 1-14, 16, 18, and 20-34 under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 4-10, 12-14, 17, 19, 21, 23, 25, 27, 29, and 31-34 of co-pending application No. 11/551,188. The Examiner rejected said claims on the grounds of non-statutory obviousness-type double patenting as being un-patentable over claims of U.S. application No. 11/551,188.

In response, applicants maintain that claims must be identical to sustain a double patenting rejection under 35 U.S.C. § 101. Applicants note that in determining "same invention" double patenting, courts ask, for each claim at issue, whether the claim in one patent or application could be literally infringed without literally infringing the claim in the other patent or application. *In re Hallman*, 655 F.2d 212, 216, 210 U.S.P.Q. 609, 612 (C.C.P.A. 1981); *In re Avery*, 518 F.2d 1228, 1232, 186 U.S.P.Q. 161, 164 (C.C.P.A. 1975); *In re Vogel*, 422 F.2d at 441, 164 U.S.P.Q. at 622.

Applicants maintain that in this instance, the claims of U.S. application No. 11/551,188 ('188) and the claims of the instant application are not identical. Applicants note that the pending claims of the instant application, as amended, are narrower in scope; and that the claims in '188 allow for a 7 member ring, wherein m=2, and the instant claims do not.

Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

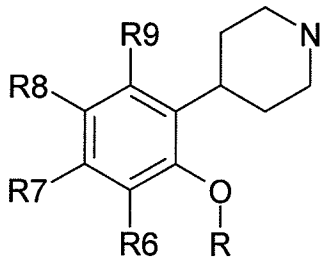
Rejection Under 35 U.S.C. § 112, First Paragraph

On page 10 of the March 5, 2007 Office Action, the Examiner rejected claims 1-14, 16, and 20-31 under 35 U.S.C. §112, first paragraph, alleging that the specification, while being enabling for certain substituents R1-R8, it does not reasonably provide enablement for the exhaustive list given. The Examiner further alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response, in an attempt to advance the prosecution of the instant application, but without conceding either the need for amendment or the correctness of the Examiner's position, applicants have amended claims 1-4, 6-11, 22, 24, 26, and 28-30 to remove alkynes and alkenes as possible substitutions for R_1-R_9.

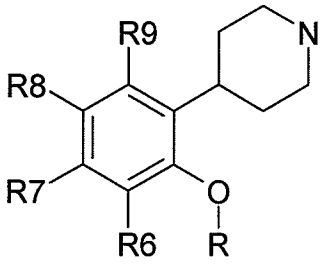
Applicants maintain that synthesis of the compounds of Formula I of claims 1-4, 6-11, 22, 24, 26, and 28-30, as amended, are enabled by the specification.

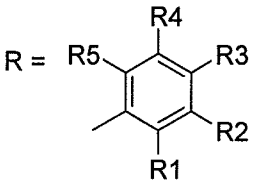
Furthermore, applicants note that, based on the teachings of the instant specification, it is well within the ordinary skill of the art to recognize that compound 5-like starting materials, i.e.:



where R= CH_3

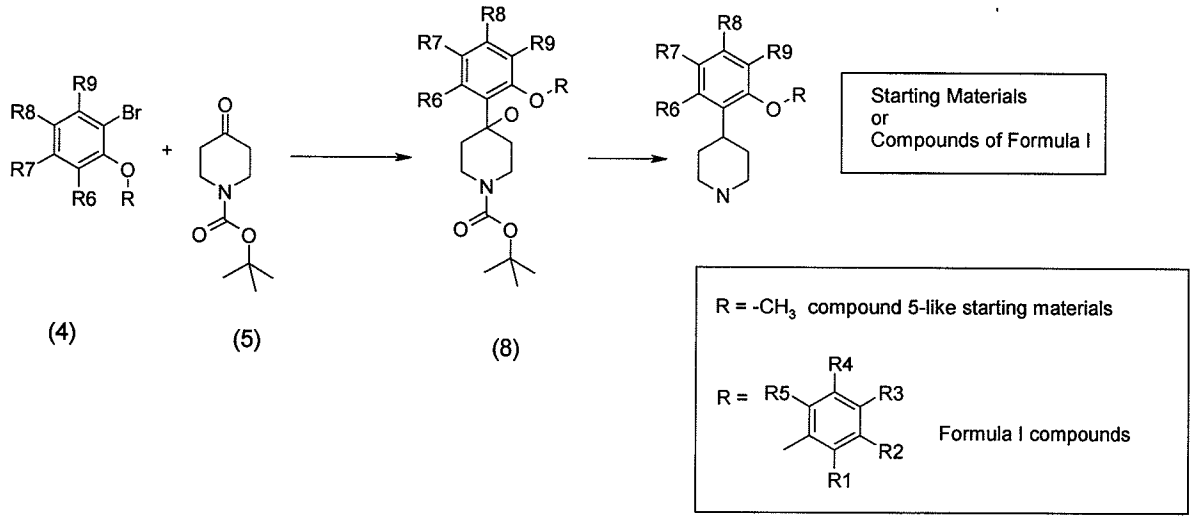
have similar structures to compounds of Formula I, i.e.:



where R = 

and thus, the same synthetic strategy and methodologies used to prepare compounds of Formula I can be used to prepare compound 5 starting materials. Certainly, no undue experimentation would be required to make such compounds. A synthesis description is provided for clarity in Scheme A below:

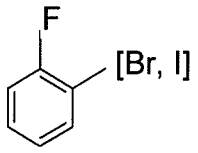
Scheme A: Synthesis Description



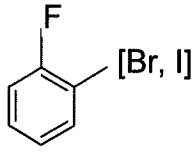
(4) (5) (8)

Note: Numbers (4), (5) and (8) above refer to formulas/compounds described in Scheme 1, on page 11 of the Office Action.

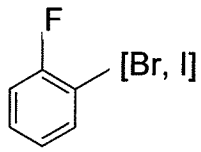
Furthermore, applicants maintain that it would be obvious to one skilled in the art that commercially available starting materials are not limited to one source only, e.g., Maybridge online catalog, as the Examiner seems to suggest. Applicants note that searches performed in SciFinder Database (American Chemical Society) resulted in



8,706 substances found containing compounds, which are used to make compound (4) above. Applicants further note that out of the 8,706 substances found, 1,795 substances were commercially available. Applicants maintain that it would be obvious to one skilled in the art to use such commercially available



compounds to further diversify subtituents R_6-R_9.

Applicants further note that methods to prepare 

intermediate compounds are well known in the art. Olah, G.A., et al. *J. Org. Chem.* **1993**, 58, 3194-3195, attached herewith as **Exhibit A**, teaches the preparation of Bromo-Iodo-benzenes and Fluoro-Iodo-benzenes. Szumigala, R.H., et al. *J. Org. Chem.* **2004**, 69, 566-569, attached herewith as **Exhibit B**, teaches the preparation of Bromo-Fluoro-benzenes.

Regarding 1-Bromo-2-Fluorobenzene derivatives, applicants note that these compounds are prevalent in the literature and their preparations are reported in the literature. Applicants further maintain that one skilled in the art would know that starting material would not be limited to what is available commercially, and would use what is reported in the literature as another source of such starting materials.

Moreover, one skilled in the art would not be limited to using 1-Bromo-2-Fluorobenzenes. Applicants direct the Examiner's attention to page 25, lines 1-6 of the specification, which mentions other methods to prepare 2-halo-diphenyl ethers. The specification cites Palmer, et al., *J. Med. Chem.* **1997**, 40, 1982-1989, attached herewith as **Exhibit C**, which teaches methods to prepare the appropriate 2-Bromo or 2-iodo diphenyl ethers, which do not require 1-Bromo-2-Fluorobenzenes.

Applicants maintain that in view of the amendments to claims1-4, 6-11, 22, 24, 26 and 28-30, and the arguments presented above, the substituents presented for R1-R9 are enabled by the specification.

Accordingly, applicants respectfully request that the Examiner reconsiders and withdraw this rejection.

On page 18 of the March 5, 2007 Office Action, the Examiner rejected claims 18 and 32-34 under 35 U.S.C. §112, first paragraph, alleging that they fail to comply with the enablement requirement. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response, applicants note that the Examiner alleges that claims are not enabled, not withstanding applicants' statements in the instant specification regarding dual activity at the Serotonin and Nor-epinephrine receptors. Applicants' statements are based on in vitro screening.

First, applicants note that section 112, First Paragraph, as explained in the 35 U.S.C. § 112 First Paragraph Enablement Training Manual (1996) places the burden on the Examiner to set forth reasonable explanation as to why claims are not enabled. Applicants maintain that without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q.367, 369 (CCPA 1971).

Applicants maintain that in this rejection, the Examiner has not met this burden. At the most, the Examiner has only referred to the general unpredictability of efficacy and safety that exists in the pharmaceutical arts. However, the courts and the United States Patent and Trademark Office (USPTO) have long held that in vivo testing of pharmaceuticals is not a requirement for patentability. In *Cross v. Iizuka*, 753 F2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), the court "perceive[d] no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question." Further, the M.P.E.P. § 2107.02 admonishes Examiners to be careful not to find evidence unpersuasive merely because no animal model for the human disease condition had been established prior to filing of the application.

Finally, although applicants are not required to submit further evidence as the instant rejection does not follow current USPTO policy or case law, applicants submit Higuchi, et al., *Neuropsychiatric Disease and Treatment,* **2007**, 30(1), 41-58, attached herewith as **Exhibit D**, for the Examiner's background information. Higuchi et al. generally teaches that the utility of milnacipran as a dual serotonin and norepinephrine reuptake inhibitor is enabled.

Accordingly, applicants respectfully request that the Examiner reconsiders and withdraw this rejection.

Rejection under 35 U.S.C. § 103(a)

On page 21 of the March 5, 2007 Office Action, the Examiner rejected Claims 1-15, 18, 20-34 under 35 U.S.C. §103(a) as being unpatentable over Elliot et al. (PCT/IB00/00108). The Examiner alleges that Elliot et al. disclose position isomers, and that the only difference is the position of the biaryl ether on the piperidine ring. The examiner further alleges that one skilled in the art, who would make applicants' compounds, would be motivated to prepare these position isomers based on the expectations that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry.

In response, applicants note that the Examiner alleges, through several pages of case law that mostly does not deal with the pharmaceutical arts, that in all cases a prior art disclosure of a positional isomer renders an applicant's claims *prima Facie* obvious.

Applicants respectfully traverse in view of the level of unpredictability that exists in the pharmaceutical arts. Apart from general and old case law, the Examiner provides

no rationale as to why the same safety and efficacy profile would be expected from the Elliot et al. reference. Elliot et al. does not teach or even mention whether the compounds disclosed therein would be improved, remain the same, or be made worse if said compounds were modified to adjust the position of the nitrogen in the six member ring. The rejection does not fill, nor explain, that gap in the prior art.

Indeed, the Supreme Court in KSR v. Teleflex has recently reaffirmed the importance of avoiding mere conclusions as the only evidence to sustain a rejection under 35 U.S.C. § 103. KSR International Co. v. Teleflex Inc., 550 U.S. __ (2007) ("rejections on obviousness grounds cannot be sustained on mere conclusory statements").

Accordingly, applicants respectfully request that the Examiner reconsiders and withdraw this rejection.

On page 26 of the March 5, 2007 Office Action, the Examiner rejected Claims 1-16, 18, 20-34 under 35 U.S.C. §103(a) as being unpatentable over Martin et al. The Examiner alleges that the only difference between the compounds of the instant case and those of martin et al. is the bioisosteric replacement of the methylene (-CH_2-) with an ether linkages (-O-).

In response, applicants respectfully traverse that the substitution of a methylene linkage with an ether linkage in Martin et al. would have been *prima facie* obvious. As a basis for this traversal, applicants incorporate all of the arguments set forth with respect to the prior rejection over Elliot et al. herein.

Further, the extremely generic disclosure of the Silverman, R. B. reference does not remedy the previously identified deficiencies. For example, the Silverman, R.B. reference only mentions in a single sentence the possibility of "broadly similar biological properties". This one statement does not begin to remove the current level of unpredictability in the drug discovery that exists. Many factors naturally affect pharmacological properties, including the structure of the overall compounds, the

exact nature of the biological target(s) (in applicants' invention there are two), and the nature of and complications associated with the disease. The references cited, and the rejection, specifically address none of these factors.

Accordingly, applicants respectfully request that the Examiner reconsiders and withdraw this rejection.

VII. Conclusion

In view of the foregoing amendments and remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the March 5, 2007 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the above-identified application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided.

No fee, other than the $1,020.00 fee for a three (3) month extension of time, is deemed necessary in connection with the filing of this Amendment, and authorization is hereby given to charge the amount of such fee to Deposit Account No. 503201. However, if any additional fee is required, further authorization is hereby given to charge the amount of any such fee to Deposit Account No. 503201.

Respectfully submitted,

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